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Balancing Antiplatelet and Anticoagulant Therapies in Patients with Cardiovascular Disease

Edward T. Carreras · Jessica L. Mega

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ABSTRACT

Anticoagulation is needed for stroke prevention in patients with atrial fibrillation. Antiplatelet therapy is essential for the prevention of stent thrombosis and the reduction of cardiovascular events in patients who undergo coronary stenting and suffer acute coronary syndromes. When these conditions overlap, the individual antithrombotic strategies are commonly combined, and the efficacy benefit of triple oral antithrombotic therapy is assumed to outweigh the bleeding risk based on the available data. Recent studies have investigated this topic further, including the first randomized controlled trial to address this issue. This new evidence challenges previous

assumptions and may have implications for future practice and investigation.

Keywords: Antiplatelet therapy and anticoagulation; Coronary stenting and atrial fibrillation; Triple oral antithrombotic therapy; Triple therapy; WOEST trial

INTRODUCTION

Of the roughly 15.4 million Americans with coronary artery disease (CAD), approximately 4.6% of them suffer an acute coronary syndrome (ACS) each year and 3.2% undergo percutaneous coronary intervention (PCI) [1]. Of those who undergo PCI, 5–7% have a preexisting indication for chronic oral anticoagulation (OAC) [2]. These patients require antithrombotic strategies that optimally balance the competing risks of bleeding, stroke, and stent thrombosis.

Prior to the common use of dual antiplatelet therapy (DAPT), approximately 6–24% of patients suffered stent thrombosis in the first year after stent placement, with a mortality rate up to 50% [3]. With the use of routine DAPT after PCI, the incidence of stent thrombosis has

E. T. Carreras (✉) · J. L. Mega
Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA
e-mail: ecarreras@partners.org

J. L. Mega
e-mail: jmega@partners.org



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averaged roughly 1–2% over the first year after PCI with a mortality rate of 10–20% [2]. OAC is equally important in atrial fibrillation (AF). The annual risk of stroke ranges 2–18% depending on patient risk factors, and warfarin provides a relative risk reduction of approximately 60%, versus just 20% for aspirin, as compared to control [4–6].

There is a paucity of evidence regarding the optimal antithrombotic strategy for patients on chronic OAC who undergo PCI. While triple oral antithrombotic therapy (TOAT) is often prescribed to maximize reductions of stroke and stent thrombosis, there is concern that the increased bleeding risk may outweigh the assumed efficacy benefit. Until recently, only a few formal recommendations for antithrombotic therapies in these patients have been published, and these recommendations have been based mostly on retrospective data and older randomized trials that studied the addition of warfarin to aspirin in ACS. Based on these data, current common practice is to use TOAT for at least a short period of time after PCI depending on patient risk factors. Recently, new evidence has emerged suggesting that other strategies may be preferred, including a randomized controlled trial (RCT) to address this topic. This review will briefly summarize the available evidence and guidelines and focus on reviewing the newer studies.

MATERIALS AND METHODS

This review article incorporates data from observational studies, review articles, available guidelines, as well as a randomized controlled trial on the use of TOAT in patients with AF and CAD. Relevant studies were obtained using a MEDLINE search for triple antithrombotic therapy, AF, and PCI. In addition, randomized

controlled trials of the use of anticoagulation and single antiplatelet therapies (SAPT) in patients with CAD were also included. Studies were chosen based on their inclusion and influence on current guidelines and practice.

DISCUSSION

Stroke Prevention in AF

AF is a common condition, with a prevalence of approximately 1% and a lifetime risk of approximately 25% after the age of 40 [5, 7]. Stroke prevention in AF is one of the most common indications for chronic OAC, which has been found to be superior to both single and dual antiplatelet therapies at reducing stroke [3]. Using the available evidence of the relative efficacy and safety of warfarin, SAPT with aspirin, and DAPT with aspirin and clopidogrel, clinicians are able to tailor stroke prevention strategies to their individual patients based on their risk factors. Table 1 depicts the relative efficacy and safety of these common antithrombotic strategies in AF, derived from the American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy for AF and based on available data from several studies and on a number of broad assumptions [3]. For most patients with at least one risk factor for stroke, the efficacy benefit of anticoagulation sufficiently outweighs the bleeding risk and is the most appropriate choice.

Antiplatelet Therapy After PCI

Antithrombotic therapy is necessary to prevent recurrent ischemic events and stent thrombosis after ACS and/or PCI. Aspirin has been long known to significantly reduce cardiovascular events after ACS [8]. Over the past decade, DAPT

Table 1 Comparison of the efficacy and safety of antithrombotic agents in atrial fibrillation

	Death, relative effect (95% CI)	Non-fatal stroke, relative effect (95% CI)	Non-fatal major extracranial bleeds, relative effect (95% CI)
Warfarin versus no Tx	0.72 (0.55–0.94)	0.34 (0.23–0.49)	2.58 (1.12–5.97)
ASA versus no Tx	0.89 (0.75–1.05)	0.79 (0.65–0.96)	1.60 (1.40–1.80)
Warfarin versus ASA	0.97 (0.85–1.12)	0.48 (0.33–0.70)	1.42 (0.89–2.29)
Warfarin versus ASA + clopidogrel	0.98 (0.79–1.22)	0.56 (0.39–0.82)	0.91 (0.67–1.23)
ASA + clopidogrel versus ASA alone	0.98 (0.90–1.07)	0.72 (0.61–0.85)	1.50 (1.18–1.89)

ASA aspirin, CI confidence interval, Tx treatment

has been studied extensively in ACS and elective PCI and found to significantly improve outcomes when compared to aspirin alone, with the majority of studies focusing on clopidogrel as the second antiplatelet agent [9, 10]. Prasugrel and ticagrelor have been the subject of more recent investigation; these agents generally achieve higher degrees of platelet inhibition than clopidogrel, do not appear to be affected by CYP2C19 polymorphisms, and have been associated with reductions in cardiovascular events after ACS with an associated increase in non-procedure related bleeding [11, 12].

Current American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines recommend at least 12 months of DAPT after PCI. Several published and ongoing trials have compared short-term (6–12 months) versus long-term (>12 months) DAPT after PCI; while the design and results of these individual trials can be debated and cross-trial comparisons are challenging, the overall results suggest a trend towards a lack of benefit of longer-term DAPT, regardless of the type of stent used [13–16]. Several ongoing trials are exploring this concept further; any change in the recommendations for DAPT duration in the future will have a

notable impact on recommendations for triple therapy in patients on OAC undergoing PCI.

Anticoagulation After ACS

The use of warfarin after ACS has been studied in several RCTs and meta-analyses [17, 18]. In the Warfarin-Aspirin Reinfarction Study (WARIS II), 3,630 patients with acute myocardial infarction (MI) were randomized to either aspirin 160 mg, warfarin with an international normalized ratio (INR) target of 2.8–4.2, or aspirin 75 mg in combination with warfarin with an INR target of 2.0–2.5 [19]. When compared to aspirin 160 mg, warfarin (rate ratio, 0.81; 95% confidence interval [CI], 0.69–0.95; $P = 0.03$) and warfarin plus aspirin (rate ratio, 0.71; 95% CI 0.60–0.83; $P = 0.001$) produced a significant reduction in the composite primary end point of death, non-fatal recurrent MI, or thromboembolic stroke. Both treatments also lead to significantly more major, non-fatal bleeding when compared to aspirin 160 mg ($P < 0.001$). The two anticoagulation arms did not differ significantly with respect to either endpoint.

The Anti-thrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) trial randomized patients to three similar arms and showed similar results to WARIS

II [20]. When compared to aspirin, high-intensity anticoagulation (hazard ratio [HR], 0.55; 95% CI 0.30–1.00; $P = 0.0479$) and aspirin plus moderate-intensity anticoagulation (HR 0.50; 95% CI 0.27–0.92; $P = 0.03$) lead to a significant reduction in the primary endpoint of death, MI, or stroke. There was no significant difference between the two anticoagulation groups with respect to the primary endpoint.

Based on the studies of warfarin in ACS, driven mostly by the results of WARIS II and ASPECT-2, warfarin was at least as efficacious as aspirin at reducing the risk of death, recurrent MI, and stroke after ACS (Figs. 1, 2) [17]. Furthermore, these studies demonstrate that warfarin alone appears to be sufficient as single therapy, and the addition of aspirin to warfarin was not found to have an additional benefit at reducing the composite endpoint of recurrent MI, stroke, or death. However, patients in these studies were not treated with modern interventional therapies, such as drug-eluting stents. As such, caution should be taken in applying these results to current practice.

Evidence and Guidelines for TOAT

A few consensus documents have been published with recommendations for TOAT, the bases for which are mostly derived from small observational studies [3, 21–26]. The available observational data show that patients receiving TOAT experienced a roughly threefold higher risk of major bleeding than did patients receiving DAPT, while the shorter versus longer durations of TOAT were associated with a twofold lower risk of major bleeding [27]. In patients with previous indications for OAC who underwent PCI, DAPT with suspension of OAC was associated with a threefold increased risk of thromboembolic events, while TOAT was associated with a lower risk of stent thrombosis and MI [27]. When analyzed in aggregate, these studies show that patients with AF who undergo PCI and suspend OAC during DAPT suffer an increased incidence of thromboembolic events when compared to either TOAT or OAC plus SAPT, while the risk of major bleeding is increased [27].

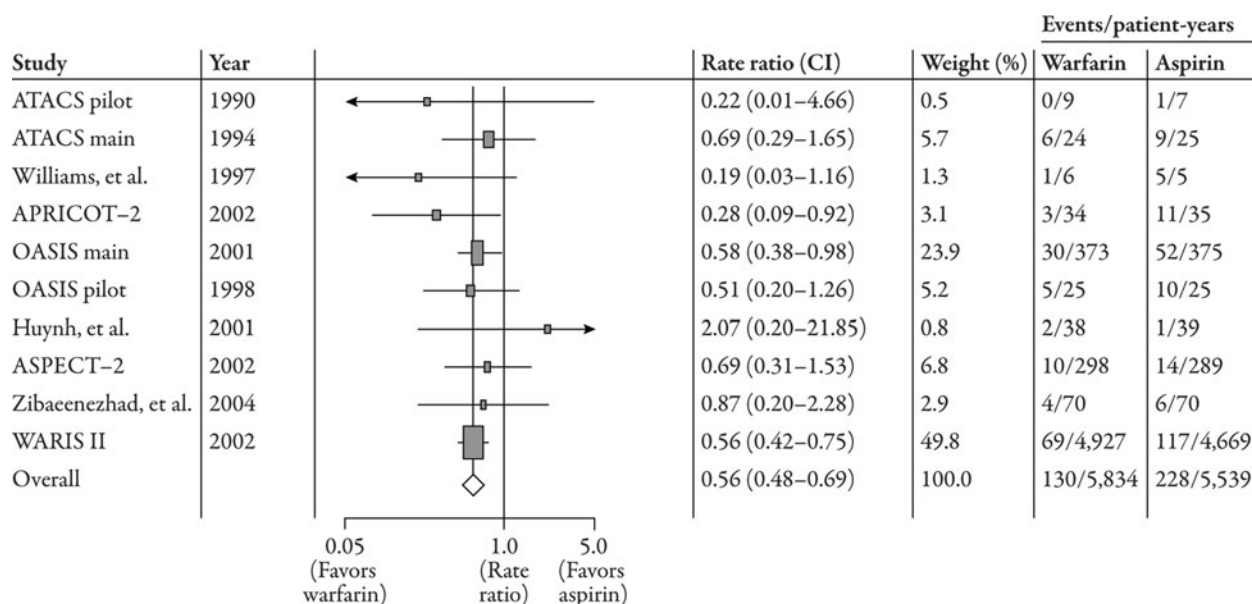


Fig. 1 Rate ratios of recurrent myocardial infarction for warfarin plus aspirin compared with aspirin alone. Figure adapted using data from Rothberg et al. [17]

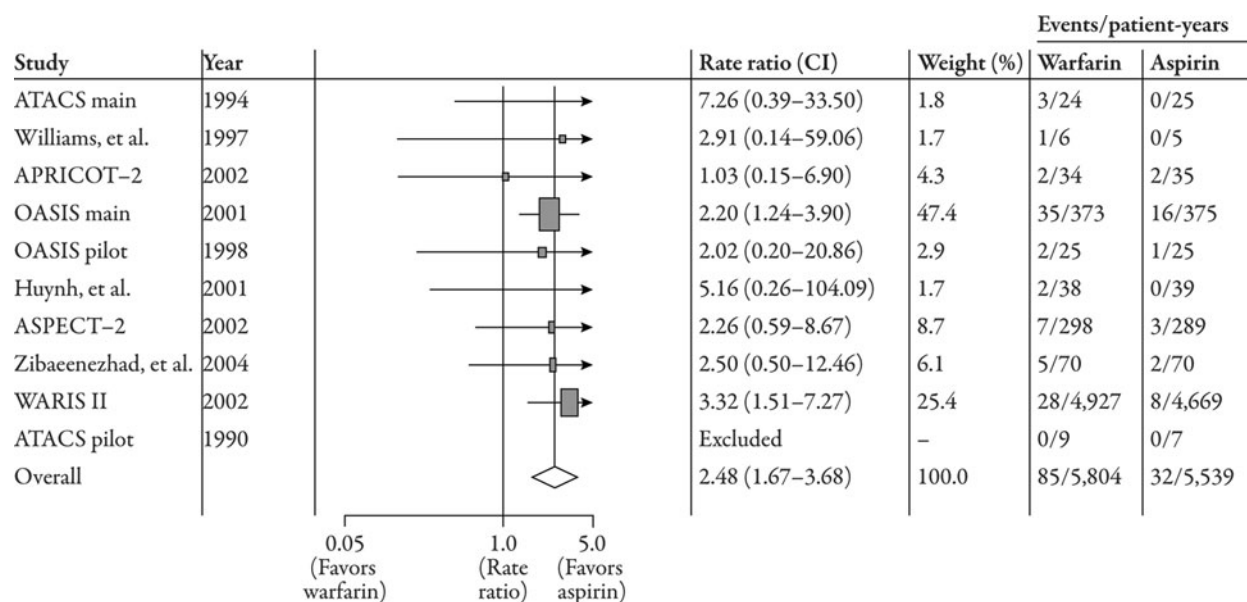


Fig. 2 Rate ratios of major bleeding for warfarin plus aspirin compared with aspirin alone. Figure adapted using data from Rothberg et al. [17]

The European Society of Cardiology (ESC) Working Group on Thrombosis makes some recommendations for the management of patients with AF who have ACS and/or undergo PCI (Table 2) [28]. In general, they advise not to stop anticoagulation and to use TOAT for a short period of time after PCI, the duration of which depends on bleeding risk and stent type. In addition, they recommended using bare metal stents, targeting an INR range 2.0–2.5 for patients receiving TOAT, and using radial access during PCI.

The ACCP published clinical practice guidelines for the management of antithrombotic therapy in patients with atrial fibrillation, including those with AF and CAD (Table 3) [3]. The authors felt that the available retrospective data were too prone to bias and instead based their recommendations on the studies of warfarin in ACS. They made several assumptions in extrapolating these data, specifically that the addition of clopidogrel to both study arms, aspirin plus warfarin and

aspirin alone, would not change the relative impacts of those treatments on death, non-fatal MI, and non-fatal extracranial bleeding. Their recommendations ultimately differ slightly from those of the ESC in that they indicate that OAC can be safely stopped for some patients at low risk of stroke while on DAPT after PCI.

Another set of recommendations was recently published in *Circulation: Cardiovascular Interventions* (Fig. 3) [2]. For patients at very low risk of stroke, the authors advise omitting OAC after PCI. For all other patients, they recommend TOAT for 1–6 months depending on risks of bleeding and stent thrombosis and stent type.

Recent Studies

Published in September, 2012, a retrospective analysis of 11,480 patients in Denmark registries studied the effect of multiple antithrombotic strategies used in AF after

Table 2 ESC recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thromboembolic risk (in whom oral anticoagulation is required)

Hemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin \geq 100 mg/day + clopidogrel 75 mg/day + gastric protection Lifelong: warfarin (INR 2.0–3.0) alone
		Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin \geq 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day ^a (or aspirin 100 mg/day)
	ACS	Bare metal/drug eluting	Lifelong: warfarin (INR 2.0–3.0) alone 6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin \geq 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day ^a (or aspirin 100 mg/day)
			Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal ^b	2 to 4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin \geq 100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0–3.0) alone
		Bare metal ^b	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin \geq 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day ^a (or aspirin 100 mg/day)
			Lifelong: warfarin (INR 2.0–3.0) alone

Adapted from Lip et al. [28]

ACS acute coronary syndrome, INR international normalized ratio, PPI proton pump inhibitors

^a Combination of warfarin (INR 2.0–3.0) + aspirin = 100 mg/day (with PPI, if indicated) may be considered as an alternative^b Drug eluting stents should be avoided

Table 3 ACCP guidelines

Stroke risk	Clinical setting	Type of stent	Recommendation
CHADS ₂ 0–1	Elective or ACS	BMS or DES	0–12 mos: DAPT After 12 mos: OAC
CHADS ₂ >1	Elective	BMS	0–1 mo: TOAT 1–12 mos: OAC + SAPT After 12 mos: OAC
		DES	0–6 mos: TOAT 6–12 mos: OAC + SAPT After 12 mos: OAC

ACCP guidelines for the management of antithrombotic therapy in patients with atrial fibrillation after coronary stenting
 ACCP American College of Chest Physicians, *BMS* bare metal stent, *DES* drug-eluting stent, *mos* months, *OAC* oral anticoagulant, *SAPT* single antiplatelet therapy, *TOAT* triple oral antithrombotic therapy

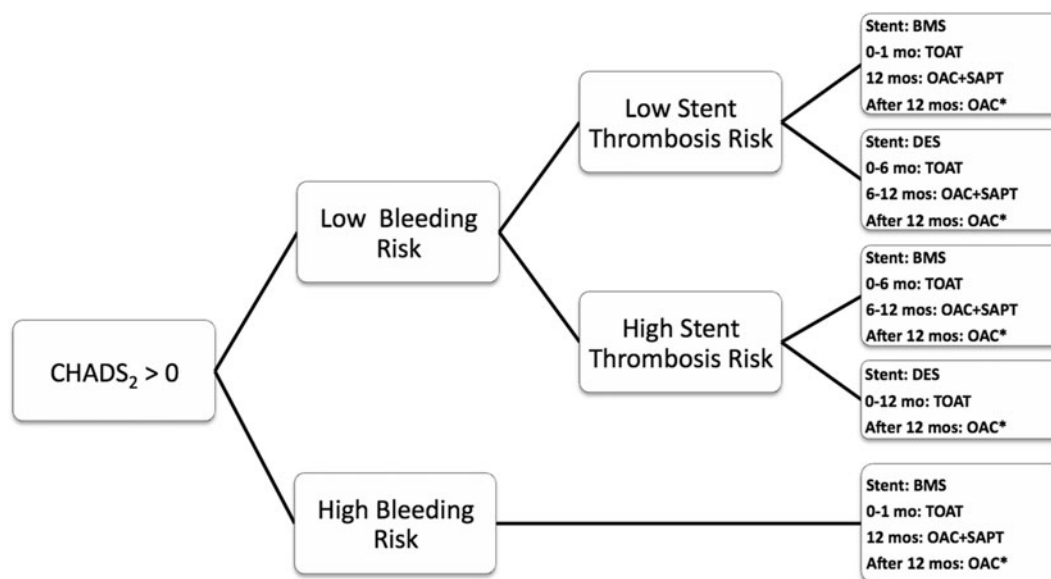


Fig. 3 Circulation guidelines for the management of antithrombotic therapy in patients with atrial fibrillation after coronary stent placement. Asterisk In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin

should be considered after 12 months. *BMS* bare metal stent, *DES* drug-eluting stent, *mos* months, *OAC* oral anticoagulation, *SAPT* single antiplatelet therapy, *TOAT* triple oral antithrombotic therapy

coronary intervention [29]. The authors found that TOAT was associated with more bleeding than vitamin k antagonist (VKA) plus SAPT at 90 days (HR 1.47; 95% CI 1.04–2.08) and 1 year (HR 1.36; 95% CI 0.95–1.95). With regard to

efficacy, TOAT and VKA plus SAPT were statistically similar (HR 1.15; 95% CI 0.95–1.40) and superior to all other strategies, suggesting that VKA plus SAPT might be preferred to TOAT.

The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) trial is a completed RCT to study the comparison of TOAT versus VKA plus SAPT [30]. The trial design and rationale were published in 2009, and the study was published in February, 2013 [30–32]. The authors randomized 573 patients undergoing PCI in an open-label, intention-to-treat design to either double therapy (warfarin and clopidogrel 75 mg) or triple therapy (warfarin, clopidogrel 75 mg, and aspirin 80 mg) in order to test the hypothesis that double therapy is superior to triple therapy with respect to bleeding. Study patients were free of any thrombolysis in myocardial infarction (TIMI) major bleeding in the past 1 year and had an indication for OAC for at least 1 year after PCI. Approximately, 70% of patients required OAC for AF; mechanical valves accounted for approximately 10%. The primary endpoint was the composite of all TIMI bleeding; the secondary endpoints included the composite of death, MI, stroke, systemic embolism, target vessel revascularization and stent thrombosis, as well as the individual components of the composite endpoints.

At 1 year, the cumulative incidence of all TIMI bleeding, which included major, minor, and minimal events, was 44.4% in the triple therapy group compared to 19.4% with double therapy (HR 0.36; 95% CI 0.26–0.50; $P < 0.0001$). The results were driven by differences in TIMI minimal and minor bleeding, with a non-significant trend towards a reduction in TIMI major bleeding seen with double therapy. There was no difference in intracranial bleeding between the two groups. The primary endpoint differences were consistent across old age, gender, ACS, indication for OAC, and stent type.

The composite of death, MI, stroke, systemic embolism, target vessel revascularization, and

stent thrombosis occurred in 17.6% of patients receiving triple therapy compared to 11.1% receiving double therapy (HR 0.56; 95% CI 0.35–0.91; $P = 0.025$). This difference was driven by a reduction in all-cause mortality, with one-year rates of 6.3% versus 2.5% in triple and double therapy, respectively (HR 0.39; 95% CI 0.16–0.93; $P = 0.027$). Rates of MI, stroke, and stent thrombosis were numerically lower in the double therapy group without statistical significance.

Integrating New Data into Practice

As previously discussed, several of the trials that studied the use of warfarin in ACS, such as WARIS II and ASPECT-2, included arms that compared warfarin alone versus warfarin plus aspirin and found no statistically significant difference in efficacy [17]. These results set a precedent to suggest that the addition of aspirin to therapeutic anticoagulation does not add significantly to the prevention of death, non-fatal MI, or stroke after ACS; however, notably, there were low rates of coronary interventions. The results of the recent Denmark registry study discussed above suggests that triple therapy provides no additional efficacy benefit while increasing bleeding when compared to VKA plus SAPT [29]. The WOEST trial results suggest that in patients on chronic OAC undergoing PCI, double therapy with warfarin and clopidogrel could be a preferred strategy with respect to mortality and bleeding when compared to TOAT with warfarin, clopidogrel, and aspirin. Thus, the WOEST results contribute further to the concept that OAC plus SAPT might be preferable to TOAT in patients with AF after PCI.

In WOEST, the increase in non-major TIMI bleeding seen with triple therapy was driven largely by gastrointestinal bleeding, skin

hematomas, and bleeding relating to access sites. Notably, proton pump inhibitors (PPIs) were used in just 25–27% of patients, and radial access during PCI was performed in only 34–39%; the authors did not encourage the use of PPIs or radial access in an effort to reproduce a more generalizable study population. The reduction in bleeding seen with double therapy was isolated to TIMI minimal and minor bleeding. However, as the authors mention, non-major bleeding episodes are clinically relevant and often lead to further complications, such as the thrombotic consequences of stopping antithrombotic therapy in response to bleeding.

The WOEST authors chose to exclude aspirin rather than clopidogrel in the double therapy group due to concern that stent thrombosis may be unacceptably increased when dropping clopidogrel. The Denmark registry study grouped VKA plus SAPT in the analysis without differentiating the choice of SAPT, but did note that an analysis of the subset of patients who received VKA plus clopidogrel yielded a bleeding risk similar to that with triple therapy. As such, there is uncertainty regarding the ideal single antiplatelet agent and further investigation is needed before declaring one strategy superior to another. To that end, a trial of patients with OAC undergoing PCI that includes arms of warfarin plus clopidogrel and warfarin plus aspirin would be useful. Prasugrel and ticagrelor also deserve mention in this setting; while the increase in bleeding associated with these agents raises concern for their use in triple therapy, it would be informative to study their efficacy as part of an OAC plus SAPT regimen in this patient population.

Caution is warranted in interpreting the WOEST efficacy results; the study was designed to evaluate safety, not efficacy, and while the composite secondary endpoint met statistical

significance, the individual components of MI, stroke, and stent thrombosis did not. The concept of dual therapy actually reducing ischemic and thrombotic events, such as stent thrombosis, is contrary to prior data; given the relatively small study population, such a conclusion should be supported by additional data.

For now, the approaches outlined by the ESC, ACCP, and *Circulation* authors offer guidance regarding TOAT, and the flow diagram in Fig. 3 above provides an approach to choose antithrombotic therapies. Based on the WOEST results, for the subset of patients at moderate to high risk of stroke, high risk of bleeding, and low risk of stent thrombosis, in whom the *Circulation* authors, for example, currently recommend one month of TOAT followed by 11 months of VKA plus SAPT, VKA plus SAPT for all 12 months may be a reasonable alternative. However, additional studies are needed to substantiate this approach. For patients at high risk of stent thrombosis, the WOEST trial does not adequately quell concerns that the risk of stent thrombosis will not be unacceptably high if one antiplatelet agent is dropped, and in these patients, a short period of TOAT is probably still reasonable. Regardless of the pharmacological approach, these patients at high risk of both stroke and stent thrombosis should receive bare metal stents whenever feasible.

Lastly, the role of newer anticoagulant agents in TOAT deserves mention, although a full discussion of this topic is beyond the scope of this paper. Dabigatran, rivaroxaban, and apixaban are the three new FDA-approved agents for stroke prevention in non-valvular atrial fibrillation, and these agents were shown to have favorable safety profiles when compared to warfarin, all leading to significant reductions in hemorrhagic stroke [33–35]. These agents, in varying doses, have been studied in ACS patients treated with background dual

antiplatelet therapy; however, subjects in these trials did not have an indication for chronic full-dose OAC (e.g., AF) [36–39]. As such, further investigation is needed to determine what role these agents may play in TOAT.

CONCLUSION

Patients on chronic OAC who undergo PCI challenge clinicians to choose the antithrombotic strategy that best balances their unique set of competing risks. Only a few formal recommendations have been published on this issue and all advise using TOAT in some patients for 1–6 months after PCI in an effort to maximize reductions of stroke and stent thrombosis. Based on available data, TOAT is assumed to provide an efficacy benefit that is superior to dual therapy and that sufficiently outweighs any increased bleeding risk of TOAT.

The WOEST trial was a RCT designed to address this issue. The results provide new groundwork for the assumption that triple therapy does yield more bleeding, while challenging prior assumptions of the efficacy benefit of TOAT. As discussed, caution should be taken with this data, awaiting further studies prior to changing practice, and only applying the results to the proper population. In time, these results may impact clinical practice and set the stage for further trials in this area.

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